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REVIEW

Circulating and Respiratory Biomarkers in Sepsis-Induced ARDS: Diagnostic and Prognostic Insights – A Narrative Review

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Abstract: Sepsis affects around 50 million people annually and is a significant contributor to acute respiratory distress syndrome (ARDS), leading to high morbidity and mortality. Sepsis-induced ARDS is the leading cause of ARDS globally and has worse outcomes compared to other causes, with mortality rates up to 40% in severe instances. Geographic variability in ARDS prevalence is notable, with rates of 27% among septic patients in China, 6–7% in Western countries, and up to 31% in sub-Saharan African Intensive Care Units, highlighting significant disparities in disease burden and outcomes. Management of sepsis-induced ARDS generally necessitates mechanical ventilation, yet extended ventilatory support can lead to negative outcomes. Weaning from ventilation is complicated by the inflammatory response and multiorgan dysfunction seen in sepsis. Traditional weaning predictors, like the rapid shallow breathing index, show inadequate sensitivity and specificity, indicating a requirement for more effective predictive tools. Recent studies have identified several biomarkers, including Pancreatic Stone Protein, soluble receptor for advanced glycation end-products, and soluble urokinase plasminogen activator receptor, as promising tools for enhancing the prediction of mechanical ventilation outcomes in sepsis-induced ARDS. Despite the identification of multiple biomarkers, a major clinical gap remains: there is currently no consensus on their routine use to guide weaning, largely due to inconsistent findings, heterogeneity in study designs, and limited large-scale validation. This review explores the role of circulating and respiratory biomarkers in improving outcomes for patients with sepsis-induced ARDS, particularly in predicting successful mechanical ventilation weaning. It appraises the evidence surrounding these biomarkers against traditional weaning indices and identifies gaps in existing research. The review emphasizes the strengths and limitations of current studies, suggesting that validated biomarker-guided strategies could significantly enhance clinical management by reducing ventilation duration, preventing extubation failures, and improving survival rates in this vulnerable patient group.

Keywords: sepsis, ARDS, biomarker, mechanical ventilation, weaning

Introduction

Sepsis is a serious illness that affects approximately 50 million people worldwide. It is defined by sudden organ failure caused by an inappropriate immune response to infection,[1,2] with fatality rates ranging from 12.5% to 31.8%.[3,4] The majority of sepsis cases are identified in hospitalized patients upon admission, particularly in emergency departments.[5] This condition can lead to significant organ impairment, especially acute renal (kidney) and pulmonary (lung) damage, frequently exacerbating Acute Respiratory Distress Syndrome (ARDS). Sepsis is the leading cause of ARDS, accounting for about 32% of cases, and it is associated with more severe outcomes compared to ARDS caused by other factors.[6,7]

According to a study conducted in China from January 2017 to May 2019, ARDS developed in 27% of 150 sepsis patients.[8] In contrast, in Western nations, the prevalence of ARDS among adult sepsis patients is approximately 6% to 7%, with a specific rate of 6.8% reported in Korea. Patients with sepsis often experience a rapid progression to ARDS,

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significantly increasing their risk of in-hospital mortality.[9] A study investigating national incidence rates and cause-specific variables for ARDS in the United States from 2006 to 2014 analyzed nearly 69 million hospital discharges, identifying 1,151,969 ARDS cases, of which 969,567 had an associated risk factor.[10]

The most common associations with ARDS were sepsis (46.7%), pneumonia (44.9%), and shock (44.4%), along with less common factors such as pancreatitis (3.4%), pulmonary contusion (1.4%), and drowning (0.2%). ARDS linked to shock and sepsis exhibited higher fatality rates compared to other etiologies. The death rate for patients with severe ARDS, defined as a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FIO2) of less than 100, was 40%, with a frequency of 10% in critical care units, affecting approximately 1 in 4 patients on mechanical ventilation (MV). Recent global research indicates that sepsis accounts for over 75% of ARDS cases, with 59% attributed to pneumonia and 16% to extrapulmonary sepsis. Each year in the United States, sepsis-induced ARDS results in around 210,000 cases, which have a higher fatality rate than other forms of ARDS.[11]

A comprehensive evaluation of 14 observational studies conducted from 2009 to 2022 in eight sub-Saharan African nations examined the prevalence and mortality rates of sepsis. In nine comprehensive hospital investigations, the aggregated prevalence was 17%, accompanied by a fatality rate of 15%.[12] The aggregated frequency in five intensive care unit (ICU) based investigations was 31%, with a notably elevated death rate of 46%. Subgroup studies revealed a hospital-wide frequency of 18% in East Africa and 20% in Southern Africa, while the prevalence in ICUs was lower, at 14% for East Africa and 13% for Southern Africa.[12] These data underscore the significant burden of sepsis and the associated elevated death rates across sub-Saharan Africa.

ARDS is a complex condition that is not primarily caused by heart failure or fluid overload. It is characterized by rapid hypoxemic respiratory failure with bilateral infiltrates and often necessitates mechanical ventilation assistance.[13–20] Although prolonged mechanical ventilation can be life-saving, it is associated with considerable complications, including ventilator-associated pneumonia (VAP), barotrauma, and diaphragm dysfunction, leading to extended ICU stays.[21,22] In patients with sepsis-induced ARDS, the timing and efficacy of discontinuing mechanical ventilation are particularly challenging due to the multifaceted pathophysiology, which encompasses systemic inflammation, multiorgan failure, and diverse patterns of pulmonary recovery.[23]

Traditional clinical weaning predictions, such as the Rapid Shallow Breathing Index (RSBI), oxygenation metrics, and spontaneous breathing trials (SBT), often exhibit limited sensitivity and specificity, particularly among the diverse cohort of septic patients.[24] Recent research has indicated that while the RSBI is a valuable tool for informing weaning choices, exclusive reliance on it may mislead clinicians.[25] The RSBI demonstrates modest sensitivity and inadequate specificity as an independent predictor of successful extubation.[24] Recently, several circulating and respiratory biomarkers have been investigated in relation to mechanical ventilation outcomes in sepsis-induced ARDS.[26–29] Biomarkers, defined as quantifiable biological substances indicative of physiological or pathological processes, have emerged as valuable tools to enhance clinical decision-making.[30–32] These biomarkers may provide real-time insights into the severity of lung damage, infection management, systemic inflammation, and organ failure,[33,34] including inflammatory cytokines[35,36] and indicators of epithelial and endothelial damage.[13,37–43]

Despite the identification of multiple biomarkers, a significant clinical gap remains: there is currently no consensus on their routine use to guide weaning, largely due to inconsistent findings, heterogeneity in study designs, and limited large-scale validation. This review explores how circulating and respiratory biomarkers may improve outcomes in patients with sepsis-induced ARDS, particularly in predicting successful liberation from mechanical ventilation. Importantly, it critically appraises the existing evidence to evaluate the value of these biomarkers in comparison to traditional weaning indices and to identify key gaps in current research. By highlighting the strengths and limitations of current studies, this review underscores the potential impact of validated biomarker-guided strategies, which could transform clinical management by reducing ventilation days, preventing extubation failures, and improving survival in this high-risk population.

Core Concepts of Pathophysiology

Sepsis is the primary factor that causes ARDS and can initiate its onset within a week, leading to a dire prognosis for affected patients.[44] ARDS is a severe condition with a fatality rate of approximately 40%, and septic ARDS demonstrates

a poorer prognosis and higher than average death rates.[44] The mechanisms underlying sepsis-induced ARDS are complex and multifaceted, involving various injurious elements such as bacterial and viral infections, trauma, and peritonitis. These factors stimulate immune cells and generate inflammatory mediators, which damage the lung endothelium and exacerbate inflammation, ultimately leading to lung injury.[6] Septic ARDS is characterized by epithelial and endothelial damage, cellular necrosis, oxidative stress, microcirculatory dysfunction, and pulmonary edema. Sepsis itself is a complex condition marked by systemic inflammation, immune dysfunction, and organ failure, with causes that include imbalances in inflammatory responses, mitochondrial damage, coagulopathy, neuroendocrine anomalies, endoplasmic reticulum stress, and autophagy, all of which contribute to organ dysfunction.[45]

Inflammation and Compromised Barrier Integrity

ARDS is a severe inflammatory disease characterized by rapid vascular damage and increased permeability of lung cells, leading to multiple organ failure.[46–48] Invasive infections stimulate immune cell activation, resulting in the release of inflammatory mediators that aggravate vascular endothelial dysfunction, thereby establishing a pro-inflammatory cycle. This process causes hyperpermeability of the pulmonary microvasculature, leading to alveolar edema and the formation of hyaline membranes.[46,49] The host's initial response involves macrophages phagocytosing pathogens and releasing pro-inflammatory cytokines. This stimulation of the innate immune system relies on pattern recognition receptors (PRRs), which are essential for recognizing damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs).[50,51] PRRs detect pathogens and damaged cells,[52,53] playing a crucial role in the immunological reaction to sepsis. Ultimately, this response can lead to mortality by triggering the release of additional inflammatory cytokines.[54,55]

Oxidative Stress

Oxidative stress occurs when there is an imbalance between antioxidants and reactive oxygen species (ROS), resulting in cellular damage.[56–59] Significant contributors to oxidative stress include air pollution and inflammation, with ROS compromising immunological function during sepsis.[60–63] Sepsis affects the innate immune system, including neutrophils and macrophages, which produce free radicals that impact cellular health.[64] Understanding free radicals as both damaging agents and signaling molecules is essential.[65]

In sepsis-induced acute lung injury (ALI), oxidants released from activated pulmonary macrophages and enzymes exacerbate inflammation and lung damage.[66] Increased peroxynitrite concentrations and oxidative stress impair immunological responses, as high mobility group box 1 (HMGB1) recruits neutrophils and macrophages, further exacerbating inflammation.[67] Alterations in T-cell metabolism also lead to increased ROS and cytokine production.[68] Interventions aimed at mitigating oxidative stress, such as overexpression of MUC1, can facilitate recovery from acute lung injury.[69] Additionally, the actions of catalase and superoxide dismutase can reduce the effects of harmful enzymes. Mice with acute lung damage caused by sepsis can recover more easily due to the Gly-Pro-Ala protein's ability to lower ROS levels and enhance superoxide dismutase activity.[70]

Vascular Endothelium

Individuals with sepsis exhibit immunological dysfunction that triggers the release of inflammatory agents, compromising capillary endothelial integrity and leading to increased pulmonary and systemic inflammation.[71] This mechanism initiates the activation and apoptosis of endothelial cells, generating pro-inflammatory signaling molecules and facilitating leukocyte accumulation, which attracts neutrophils, macrophages, and T cells.[72] The accumulation of leukocytes, particularly neutrophil-platelet aggregates, demonstrates complex thrombo-inflammatory characteristics.[73] Alveolar macrophages play a vital role in lung inflammation; their loss exacerbates ARDS by promoting neutrophil migration and increasing cytokine levels.[74–78] Vascular endothelial (VE)-cadherin and endothelial receptor kinase (TIE2), regulated by vascular endothelial protein tyrosine phosphatase (VE-PTP), are crucial for maintaining the integrity of vascular endothelial cells.[79,80] Cytoskeletal connections, guanosine triphosphate (GTP)ases, and phosphorylation influence their functionality.[81] Inflammatory responses can undermine VE-cadherin, but actin filaments and stress fibers help preserve cell junction integrity.[82–84]

Injury to Alveolar Epithelium

ARDS is primarily triggered by damage to the alveolar epithelium, with its severity influenced by the exudative phase.[13] This damage results in immune cell-mediated pulmonary injury,[72] generating pro-inflammatory mediators and necessitating lung-protective breathing.[11,85] The alveolar epithelium, composed of type I and type II cells, is essential for fluid clearance and pulmonary gas exchange.[86] In ARDS, alveolar injury is predominantly caused by the death of these cells. Type I cells, which are crucial for gas exchange, establish tight junctions,[87] while type II cells promote repair and regeneration of lung tissue.[88,89] Strategies aimed at attenuating apoptosis and employing mesenchymal stem cells may enhance therapeutic outcomes for ARDS.[90–92]

Cellular Mortality

Defective neutrophil-macrophage efferocytosis in ARDS increases secondary necrosis and the generation of inflammatory mediators,[93] while oxidative stress and mitochondrial dysfunction exacerbate lung disorders by inducing apoptosis and necroptosis.[94–96] Excessive apoptosis pathways may contribute to the disease's pathogenesis.[97] Cell death, which can be categorized into apoptosis and necrosis, is essential for maintaining the equilibrium of multicellular organisms and their defense against pathogens or nutrient deficiency.[98] Apoptosis is characterized by cytoplasmic vacuolation, nuclear condensation, and plasma membrane blebbing.[99]

Programmed Cell Death

Apoptosis occurs through intrinsic and extrinsic mechanisms, leading to the activation of caspases.[100] Intrinsic apoptosis in the lung may be initiated by the withdrawal of growth factors, oxidative stress, endoplasmic reticulum stress, and DNA damage, thereby enhancing pro-survival signaling pathways, including those mediated by protein kinase B.[101] Anoikis is caused by the loss of integrin-mediated adhesion,[102] whereas DNA damage, oxidative stress, and death receptor signaling lead to intrinsic and extrinsic apoptosis, respectively.[103,104] Necroptosis is a controlled necrotic process triggered by tumor necrosis factor receptor 1 (TNFR1)-mediated receptor-interacting protein kinase 1 (RIPK1)-RIPK3 activation and necrosome formation.[105,106]

Pyroptosis

Programmed cell death mediated by inflammation has been well investigated for its role in the progression from ARDS to pulmonary fibrosis.[107] Pyroptosis is a type of programmed necrotic cell death driven by gasdermins, whose proteolytic cleavage facilitates the formation of pores.[108] Gasdermin D is activated by inflammasomes, although other family members may be activated independently of this process. While pyroptosis aids in pathogen defense, its excessive activation can lead to cytokine storms, inflammation, and tissue damage, resulting in conditions such as sepsis, ARDS, atherosclerosis, and neurodegeneration.[109] The NLRP3 inflammasome-mediated pyroptosis in ARDS creates membrane pores and releases pro-inflammatory cytokines after infections or trauma activate alveolar macrophages.[110–116]

Ferroptosis

Sepsis impairs iron metabolism and lipid peroxidation, potentially leading to metabolic disorders, including ferroptosis, a cell death pathway dependent on iron associated with ARDS.[117,118] In cases of acute pancreatitis, sepsis can induce ferroptosis in intestinal epithelial cells, weakening the barrier and allowing the movement of bacteria and toxins.[119] This process is exacerbated by respiratory infections caused by Pseudomonas aeruginosa.[120] Early immunological responses lead to iron and lipid peroxidation during macrophage activation, initiating ferroptosis.[121] Additionally, infection with Mycobacterium tuberculosis causes glutathione depletion, iron overload, and downregulation of glutathione peroxidase 4 (GPX4),[122] all of which affect the survival and functionality of CD8 T cells.[123]

Oxidative stress is associated with the pathophysiology of ARDS, as infections may stimulate ROS generation, altering the balance between oxidative and antioxidant capabilities. Redox imbalance can induce ferroptosis,[124] leading to immune cell activation and the generation of pro-inflammatory cytokines, which aggravate lung injury and render ferroptosis an immunogenic form of cell death.[125] Lipopolysaccharide (LPS) treatment may inhibit the expression of

GPX4 and SLC7A11 in sepsis-induced ARDS while elevating levels of malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and total iron, thus reversing these alterations.[126]

Immunologic Mechanism

Sepsis-induced ARDS results from a complex interplay of systemic infection, immunological dysregulation, and pulmonary damage. The immunological pathways are characterized by an initial hyperinflammatory phase induced by innate immune activation, followed by an immunological response that is either suppressed or dysregulated, leading to ongoing tissue damage and organ failure.

Initiation by Pathogen Recognition

The innate immune system's identification of pathogens is the first step in the development of sepsis-induced ARDS.[127] Macrophages phagocytose pathogens, release pro-inflammatory cytokines, and trigger a cytokine storm, thereby initiating the innate immune response.[50,128] Immune cell stimulation by pattern recognition receptors damages the alveolar space, resulting in the accumulation of edema fluid.[51,86] Negative feedback systems and immunological fatigue can lead to immune paralysis in later phases, impacting the host's hyperimmune state.[129]

Cytokine Storm and Inflammatory Cascade

Severe sepsis results from a cytokine storm.[130] Most rat models primarily focus on general sepsis and fail to accurately represent severe sepsis, which is characterized by increased early mortality within the initial 72 hours.[131] Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are important indicators of the degree of inflammation.[132] Immunological complexes, bacterial infections, and endotoxins can cause alveolar epithelial cells to undergo apoptosis[133] and cease proliferating,[134,135] accelerating the progression of sepsis-associated ALI.[136] Pharmacological suppression of alveolar epithelial cell apoptosis has shown effectiveness in reducing acute lung injury in animal studies, thereby enhancing survival outcomes.[137] The distinction between normal and dysregulated inflammation in severe infections can be ambiguous, as many cytokines exert both protective and detrimental effects.[138,139] When cytokine levels exceed a certain threshold, reversing the cytokine storm becomes challenging, and the intricate interactions of mediators further complicate this limit.[139] A severe inflammatory cascade could be triggered by the dysregulated cytokine storm, leading to either irreversible or reversible end-organ damage and possibly death.[140] Chronic illnesses may precipitate sepsis via inflammatory cascade responses and cytokine storms. IL-6, a pivotal factor in the cytokine storm, and its associated signaling pathways have been recognized as essential factors in sepsis.[141] The inflammatory cascade progressively escalates, resulting in sepsis driven by a cytokine storm. Activation of the IL-6-associated signaling system renders some chronic illnesses susceptible to sepsis due to persistent low-grade inflammation. Conversely, sepsis may exacerbate these chronic conditions, resulting in multiple organ failure.[141]

Physiological Role and Pathophysiological Significance of Emerging Biomarkers

Interleukin-6 (IL-6)

IL-6 regulates numerous physiological processes, including cell proliferation, differentiation, survival, and apoptosis. It is essential for the functioning of the immune and hematopoietic systems, influencing various other systems such as neurological, endocrine, and bone metabolism.[142] Synthesized primarily by myeloid cells, including macrophages and dendritic cells, IL-6 is produced in response to pathogen recognition via toll-like receptors(TLRs).[143] It is vital for the proliferation of myeloma cells and the survival of plasma blasts during the adaptive immune response, promoting plasma cell differentiation and enhancing antibody synthesis.[143]

Originally identified as B-cell stimulatory factor 2 (BSF-2), IL-6 also stimulates immunoglobulin production in activated B cells.[144,145] Rapidly synthesized in reaction to infections or tissue damage, IL-6 facilitates host defense by regulating acute-phase responses and hematopoiesis.[146–149] Furthermore, the IL-6 family of cytokines helps maintain the balance between pro-inflammatory and anti-inflammatory responses, augments thermogenesis, inhibits diet-induced obesity, and ameliorates insulin resistance through interactions with adipocytes and activation of the p38 mitogen-

activated protein kinase (MAPK) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) signaling pathway.[150]

Despite its essential physiological functions, excessive production of IL-6 can lead to significant pathophysiological consequences.[151] Overproduction of IL-6 is associated with systemic inflammatory response syndrome (SIRS) and cytokine-release syndrome (CRS), conditions characterized by hyperinflammation.[148,152] In sepsis, IL-6 contributes to a cytokine storm, which entails dysregulated immune responses marked by the simultaneous activation of numerous cytokine networks.[153] This hyperactive state can exacerbate feedback loops, resulting in tissue damage, multi-organ failure, and increased mortality.[151] Additionally, IL-6 plays a critical role in endothelial dysfunction during sepsis-induced ARDS by activating endothelial cells and enhancing vascular permeability. This leads to the effusion of fluid and proteins into the alveolar space, contributing to respiratory failure.[154,155] Ultimately, while IL-6 is vital for normal immune function and metabolic regulation, its dysregulation can significantly impact health, underscoring its dual role in both protective and pathological processes.[153]

Angiopoietin-2 (Ang-2)

Ang-2 is a growth factor that is part of the angiopoietin/Tie signaling pathway, which is crucial for angiogenesis. It was discovered after the identification of angiopoietin-1 (Ang1) through complementary DNA (cDNA) library screening.[156] Structurally, Ang-2 is a 496-amino-acid protein that shares approximately 60% similarity with Ang1, though it lacks one of the nine cysteine residues present in Ang1. Ang2 features a secretion signal peptide, an NH2-terminal coiled-coil domain, and a COOH-terminal fibrinogen-like domain.[157] Under physiological conditions, Ang2 functions in an autocrine manner with tightly regulated expression. It binds to the Tie2 receptor with an affinity similar to that of Ang1 but typically acts as an antagonist, inhibiting Ang1-mediated phosphorylation of Tie2 in blood endothelial cells (BECs).[157] Interestingly, Ang2 can also weakly phosphorylate Tie2, enhancing endothelial functions.[158,159] The Tie1 receptor modulates Ang2's activity, converting it from an antagonist to an agonist during inflammation following Tie1 cleavage.[160] While Ang2 is not essential for embryonic blood vessel development, it plays a significant role in modulating angiogenic sprouting and vascular regression, particularly in neonates.[161]

In pathological contexts, the dysregulation of Ang2 has significant implications. Its expression is induced by inflammatory mediators, such as thrombin, as well as by conditions like hypoxia and malignancy.[162–166] Ang2 compromises endothelial integrity, although this effect can be countered by Ang1 or vascular endothelial growth factor (VEGF). In pathological settings, Ang2 facilitates angiogenesis independently of Tie2 or Ang1, promoting endothelial cell migration and tube formation.[167,168] This is particularly evident in conditions associated with increased vascular permeability and angiogenesis, where overexpression of Ang2 can lead to larger tumors and increased metastasis, while inhibition of Ang2 has the opposite effect.[169–171]

Ang2 is also implicated in various inflammatory disorders, including autoimmune diseases and acute lung injury.[172,173] It induces vascular permeability through interactions with cell junction proteins such as integrins and vascular endothelial cadherin (VE-cadherin). Ang2 is essential for initiating the inflammatory response, as shown by the inability of Ang2-deficient mice to mount such responses in infection models. Elevated levels of Ang2 in the blood correlate with inflammatory markers, suggesting its potential as an inflammatory biomarker.[174] For example, patients with pneumonia exhibit increased Ang2 levels, particularly among those who do not survive 28 days post-diagnosis.[175] Furthermore, Ang2 plays a critical role in endothelial function and cardiovascular remodeling. Increased levels of Ang2 are associated with conditions such as coronary heart disease and congestive heart failure.[176–179] It serves as a biomarker and influences post-stroke recovery by initially increasing detrimental vascular permeability, which later correlates with microvessel maturation after one week.[180] Ang2 also facilitates the differentiation and migration of brain progenitor cells independently of Tie2.[181] Additionally, a reduction in Ang2 alongside an increase in Ang1 promotes vascular remodeling, indicating potential therapeutic targets for post-stroke interventions and improved cardiac allograft outcomes by mitigating endothelial cell activation and leukocyte infiltration.[182]

Pancreatic Stone Protein (PSP)

PSP, also known as lithostathine or Reg protein, is a glycoprotein composed of 144 residues, primarily synthesized by the exocrine pancreas.[183,184] It is also detected in the endocrine component of the regenerating pancreas and in certain tumors, including pancreatic ductal cell carcinoma and colorectal tumors.[185–187]Although the precise physiological role of PSP remains somewhat ambiguous, it has been shown to promote islet regeneration in partially depancreatized rats,[188] suggesting its potential function as a β-cell growth factor that helps preserve β-cell mass and functionality.[189,190] Additionally, PSP regulates pancreatic enzyme secretion, thereby assisting in digestion and nutrient absorption, which contributes to overall gastrointestinal health.[183] In pancreatic juice, the presence of lithostathine indicates a potential role in inhibiting stone formation by modulating the nucleation, development, and aggregation of calcite crystals. Specifically, lithostathine impedes crystal nucleation and restricts the development of pre-existing calcium carbonate (CaCO3) from supersaturated solutions, while also functioning as a modulator of calcite crystal habit, leading to the formation of smaller crystals.[191,192]

In pathological contexts, dysregulation of PSP is observed, particularly in conditions such as sepsis. The inflammatory response associated with sepsis may compromise PSP function, as elevated pro-inflammatory cytokines can lead to pancreatic dysfunction and negatively impact pulmonary health.[193] Sepsis often precipitates acute pancreatitis, which can further exacerbate lung damage. In this setting, dysregulation of PSP may contribute to the formation of pancreatic stones, resulting in duct obstruction and an increased risk of inflammation affecting other organs, including the lungs.[194] Similarly, decreased levels of PSP in chronic pancreatitis may promote pancreatic stone development, duct obstruction, and heightened inflammation and discomfort.[194]

Pancreatic duct obstruction leads to elevated duct pressure and permeability, facilitating the passage of macromolecules, such as pancreatic enzymes, through the typically impermeable duct. This increased permeability, along with morphological alterations, is likely linked to elevated secretory pressure during blockage, fostering inflammation and injury.[195] Consequently, PSP may modulate the inflammatory response associated with pancreatic disorders, where its dysregulation could exacerbate chronic inflammation in diseases such as pancreatitis and pancreatic cancer.[196]

Syndecan-1 (Sdc-1)

Sdc-1 is a heparan sulfate proteoglycan that plays a crucial role in various physiological processes, including host defense, angiogenesis, leukocyte recruitment, microbial interactions, and matrix remodeling.[197] It is particularly significant in regulating protein leakage in the intestinal epithelium, smooth muscle cell proliferation during vascular injury, keratinocyte proliferation in dermal injury, and lipoprotein metabolism.[198–201] Sdc-1 is generally absent from most leukocytes, except for active macrophages, but serves as a hallmark for plasma cells and B cell malignancies.[202,203]

During inflammation, Sdc-1 negatively regulates leukocyte adhesion and migration by inhibiting integrin interactions with endothelial intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). This function is vital for controlling the inflammatory response and ensuring appropriate immune cell trafficking. Additionally, research has shown that syndecan-1 shedding can facilitate the resolution of neutrophil inflammation by aiding in the removal of sequestered CXC chemokines in a heparan sulfate-dependent manner.[204] The pathophysiological significance of Sdc-1 is highlighted by the severe symptoms observed in syndecan-1 null animals during various illness challenges.[197] The absence of Sdc-1 can lead to detrimental outcomes in multiple contexts. For example, in cardiac tissue remodeling following myocardial infarction, Sdc-1 deficiency results in poor collagen cross-linking, impaired cardiac function, disorganized collagen matrices, increased inflammatory cell infiltration, and elevated matrix metalloproteinases (MMP-2 and MMP-9) activity.[205,206] These changes contribute to adverse cardiac remodeling and poorer healing outcomes. Conversely, the overexpression of syndecan-1 has been shown to be critical for effective cardiac tissue remodeling by reducing inflammation and protecting against heart degeneration. This illustrates the dual role of Sdc-1, where both its presence and absence can significantly impact disease outcomes.[206]

Presepsin (P-SEP)

P-SEP is a soluble form of CD14, a co-receptor that plays a critical role in the immune response to bacterial infections. It is released into the bloodstream when bacteria and antigens interact, remaining stable in circulation. P-SEP serves as a readily measurable biomarker for systemic infections, particularly in their early stages.[207] The immune system relies on its ability to recognize and respond to infections through both innate and adaptive immunity. While adaptive immunity takes time to develop, innate immunity provides immediate defense through mechanisms such as phagocytes and antimicrobial peptides. Innate immunity utilizes PRRs,[208] including TLRs, to identify conserved PAMPs and trigger an immediate immune response.[209] CD14, as a co-receptor, binds specifically to ligands like bacterial lipopolysaccharides (LPS).[210,211] For effective recognition of LPS, CD14 requires interaction with lipoprotein binding protein (LBP), which facilitates its presentation. This interaction activates TLRs, leading to the generation of cytokines and the initiation of phagocytosis by monocyte-macrophages. Although CD14 itself lacks a transmembrane domain and cannot independently transmit signals, it is essential for forming complexes with LPS and TLRs, enhancing intracellular signaling and host defenses.[209,212]

The pathophysiological significance of P-SEP is underscored by its role as a biomarker for sepsis and other systemic infections. Following the proteolytic cleavage of CD14, soluble CD14 fragments, particularly sCD14-ST, enter the bloodstream and serve as indicators of an immunological response.[213] Elevated levels of circulating soluble CD14 (sCD14) correlate with the severity of sepsis in both adults and neonates, making it a valuable tool for detecting systemic illnesses associated with Enterobacteriaceae.[214,215] P-SEP was first identified as a diagnostic biomarker for septic patients in 2005 due to its significant increases in blood plasma during the early stages of sepsis.[216] Its potential as a sepsis biomarker has been further validated by the development of a one-step test for routine evaluation of presepsin levels. The measurement of presepsin in clinical settings can aid in early diagnosis and management of sepsis, ultimately improving patient outcomes.[213,217]

Endocan

Endocan is a recently identified dermatan sulfate proteoglycan primarily found in serum and expressed in activated endothelial cells.[218] Its expression is influenced by various growth factors, including vascular endothelial growth factor (VEGF-A and VEGF-C), hepatocyte growth factor (HGF/MET), fibroblast growth factor (FGF-2), and epidermal growth factor receptor (EGFR). These factors act through several signaling pathways, such as protein kinase C (PKC)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), phosphoinositide 3-kinase (PI3K)/Akt, and Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3), to elevate endocan expression.[219,220] In healthy physiological conditions, endocan plays a role in promoting angiogenesis and vascular integrity. It facilitates leukocyte recruitment and adhesion, which are essential for angiogenesis and inflammatory responses.[221] Endocan increases the release of adhesion molecules such as VCAM-1, ICAM-1, and E-selectin from inflammatory endothelial cells, contributing to the regulation of immune responses and vascular homeostasis. Additionally, endocan may serve as a biomarker for endothelial activation.[222–225]

The pathophysiological significance of endocan is highlighted by its correlation with various conditions, including vascular disorders, systemic inflammation, and several types of cancer. Elevated levels of endocan are associated with atherogenesis, as it promotes the synthesis of nitric oxide, reactive oxygen species, and inflammatory mediators like inducible nitric oxide synthase (iNOS) and C-reactive protein (CRP).[226] Proinflammatory cytokines, such as TNF-α and IL-1β, enhance endocan expression by activating inflammatory pathways like NF-κB.[227,228] This upregulation contributes to vascular inflammation and the progression of various diseases.[221] Endocan also plays a role in modulating leukocyte behavior; it can inhibit leukocyte migration by binding to integrin CD11a/CD18 (LFA-1), potentially mitigating acute lung inflammation.[229] The P14 fragment of endocan, generated by cathepsin G, facilitates leukocyte extravasation by competing for LFA-1 binding, with elevated levels observed in sepsis patients, indicating its potential as a marker of neutrophil activation.[230,231] Research has shown that endocan reduces inflammation markers such as TNF-α and IL-6 and decreases LPS-induced apoptosis in pulmonary epithelial cells. Lower levels of endocan in individuals with ARDS and acute lung injury suggest its significant role in respiratory inflammation and its potential as a therapeutic target.[232]

Soluble Receptor for Advanced Glycation Endproducts (sRAGE)

sRAGE is a member of the immunoglobulin superfamily located in the Class III region of the major histocompatibility complex.[233,234] Initially recognized for its affinity for advanced glycation endproducts (AGEs), RAGE has since been reclassified as a PRR due to the discovery of several additional ligands, including DAMPs.[235,236] Under normal physiological conditions, RAGE is typically expressed at low levels in differentiated adult cells. However, its expression is significantly elevated in mature lung type I pneumocytes, where it may play a role in maintaining lung function and responding to injury.[237]

RAGE is associated with a variety of inflammation-related disorders, including vascular disease, cancer, neurodegeneration, and diabetes.[238,239] Its involvement in these conditions is primarily due to its role in mediating inflammatory responses. When activated by its ligands, RAGE can trigger pro-inflammatory signaling pathways, leading to increased inflammation and tissue damage. Interestingly, RAGE expression is significantly reduced in lung tumors and idiopathic pulmonary fibrosis compared to levels found in healthy tissue, suggesting a complex role in these diseases. The downregulation of RAGE in such contexts may indicate a loss of its protective functions or a response to chronic inflammatory states.

Soluble Urokinase Plasminogen Activator Receptor (suPAR)

suPAR is a soluble variant of the membrane-bound receptor uPAR, which is primarily found on the surfaces of immune cells, including monocytes, macrophages, activated T-lymphocytes, endothelial cells, and certain cancer cells.[240] The uPAR plays a crucial role in plasminogen activation and fibrinolysis, influencing key cellular processes such as proliferation, migration, adhesion, angiogenesis, and the inflammatory response.[241] The expression of the PLAUR gene, which encodes uPAR, is typically low but increases in response to immunological activation, inflammation, and tumor growth. This upregulation is driven by the activation of innate immune receptors that induce transcription factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1), promoting PLAUR gene expression.[240] suPAR is released into the bloodstream through the proteolytic cleavage of uPAR and can be detected in various bodily fluids, including blood plasma, serum, cerebrospinal fluid, saliva, and urine.[242–244] Its levels in the bloodstream correlate positively with total white blood cell counts and are associated with both innate and adaptive immune cells,[245,246] particularly neutrophils, monocytes, and eosinophils.[245,247–249]

In pathological contexts, elevated levels of suPAR are associated with various inflammatory conditions and diseases. The expression of uPAR and the subsequent release of suPAR can be stimulated by inflammatory mediators such as LPS, IL-8, TNF-α, granulocyte colony-stimulating factor (G-CSF), and formyl-methionyl-leucyl-phenylalanine (fMLP).[250,251] For instance, LPS injection in healthy individuals leads to increased uPAR expression on monocytes and elevated suPAR levels in the bloodstream.[252,253] Additionally, interleukin-1 beta (IL-1β) promotes suPAR release from endothelial and vascular smooth muscle cells, although IL-6 can inhibit LPS-induced suPAR release.[254–257]

The binding of uPAR to its ligand, urokinase plasminogen activator (uPA), on immune cells is critical for cell migration during inflammation and immune responses. Active uPA catalyzes the conversion of plasminogen to plasmin, initiating a cascade that activates matrix metalloproteinases, which degrade extracellular matrix components.[241,258] This process accelerates extracellular matrix disintegration, activates growth factors, enhances cell migration, facilitates fibrinolysis, causes vasodilation, increases vascular permeability, and aids in the opsonization and phagocytosis of pathogens.[241,259,260]

Elevated suPAR levels have been linked to various inflammatory diseases, including infections, autoimmune disorders, and cancer. In particular, suPAR is predominantly expressed in pro-inflammatory monocyte subsets during acute liver failure and is released from monocytes following LPS stimulation, highlighting its role in the immune response.[261] The correlation between suPAR levels and innate immune cells underscores its potential as a biomarker for inflammation and disease progression.

Clinical Challenges in Weaning from Mechanical Ventilation

Mechanical ventilation (MV) is an essential life-saving intervention for severely ill patients. However, 20% to 40% of these individuals encounter problems during the weaning process, experiencing varying levels of strain (Table 1).[262] Although MV is associated with potential complications, prompt weaning from ventilation is crucial once the underlying disease has fully recovered and the patient demonstrates the ability for spontaneous, unassisted respiration.[263] Despite its advantages, this treatment approach may lead to several types of harm, including ventilator-induced lung Injury(VILI), VAP, tracheal injuries, and neurodevelopmental abnormalities (Table 1).[264,265]

Weaning from mechanical ventilation involves the systematic reduction of ventilatory assistance, while emancipation refers to the complete cessation of support for patients deemed ready. The weaning method began in the 1960s, initially employing a T-piece connected to the endotracheal tube for oxygen administration to progressively increase the duration of spontaneous breathing.[266] Subsequently,Intermittent Mandatory Ventilation (IMV) and Synchronized Intermittent Mandatory Ventilation (SIMV) were introduced. These methods have become fundamental to prevalent weaning procedures, although they lack substantial high-quality data to validate their effectiveness. SIMV allows for a gradual decrease in the number of mandatory breaths, enabling patients to engage in more spontaneous breathing, thereby facilitating a smoother transition. The introduction of Pressure Support Ventilation (PSV) provided enhanced assistance for spontaneous breaths during SIMV; alternatively, PSV may serve as the sole mode of support, with weaning achieved by gradually reducing the pressure support level.[266]

The optimal outcome of weaning is successful extubation; however, some patients may require a tracheostomy before being liberated from ventilator support. It is important to distinguish between ventilator release (the discontinuation of all invasive support) and extubation (the removal of the endotracheal tube), as these are separate procedures. The count of ventilator-free days, typically assessed over a 28-day period, reflects the duration during which patients are not reliant on artificial ventilation.[290]

A SBT evaluates a patient's ability to breathe with minimal or no ventilatory assistance. It is recommended that SBTs commence whenever the primary cause of respiratory failure appears to be addressed; however, there is no consensus on the criteria for assessing the reversal of the underlying condition.[267] Clinicians often utilize a combination of subjective evaluations and objective indicators, including improved gas exchange, cognitive state, neuromuscular function, and

Table 1 Clinical Challenges in Weaning from Mechanical Ventilation

Domain	Key Points	Implications/Outcomes	Limitations/Challenges
Weaning challenges	20–40% of patients experience difficulty during weaning[262]	Prolonged MV, higher ICU stay.	Variability in patient response; underlying disease heterogeneity
MV-Associated Complications	VILI,VAP, Tracheal injury, neurodevelopmental issues.[264,265]	Increased mortality and morbidity	Risk persists despite adherence to protocols
Weaning strategies	T-piece,IMV,SIMV,PSV.[266]	Gradual transition to spontaneous breathing	Lack substantial high-quality data to validate their advantages
SBT	Assesses readiness for extubation[267,268]	Guides ventilator liberation	Passing SBT does not guarantee successful extubation; secretions, cough weakness may impede success
Prediction Scores	RSBI <105, Morganroth, CROP, HACOR, WEANS NOW, ExPres[269–286]	Assist in weaning decisions	RSBI affected by fever, anxiety, COPD, CHF, tube size; composite scores complex or not widely validated
Extubation Failure & Reintubation	2–30% reintubation; predictors: high secretions, $PaCO_2$ >5.99 kPa, prolonged MV, upper airway issues[287]	Longer MV duration, higher tracheostomy rates, increased mortality	Multifactorial etiology; early extubation may increase risk; age >70, sedation, anemia
Other Considerations	Ventilator-free days, hemodynamic stability, lung mechanics, mental status[288,289]	Measures success of liberation and patient recovery	Objective and subjectives indicators may not always align; threshold values may vary depending on PSV vs T-piece

Abbreviations: MV, mechanical ventilation; VILI, Ventilator induced lung injury; VAP, Ventilation associated Pneumoniae; IMV, Intermittent Mandatory Ventilation; SIMV, Synchronized Intermittent Mandatory Ventilation; PSV, Pressure Support Ventilation; CHF, Congestive Heart Failure.

imaging results. It is acknowledged that some patients may be effectively weaned even if they do not meet all criteria completely.[267] Successfully passing an SBT does not guarantee effective extubation or complete ventilator release, as factors such as excessive secretions and reduced cough reflexes may compromise the results. Research indicates that only 55% of patients who successfully completed an SBT were extubated without requiring another trial.[268] Re-intubation is necessary in approximately 2% to 30% of patients following a scheduled extubation, which correlates with prolonged ventilation, an increased likelihood of tracheostomy, a higher incidence of VAP, and elevated mortality rates.[291] The standard protocol for SBT failure includes assessing reversible factors, optimizing the patient's physiology, and conducting another SBT the following day.[288] Failure often arises from cardiovascular issues or problems with the respiratory pump.[292,293] Extubation failure, commonly due to an inability to manage respiratory demands, is associated with higher mortality rates from complications such as aspiration and pneumonia.[294,295] Although mortality is minimal (11%) in cases of upper airway obstruction, it can increase significantly (36%) in other circumstances.[296]

Key predictors of extubation failure include high secretions, arterial carbon dioxide tension exceeding 5.99 kPa, prolonged mechanical ventilation lasting more than 72 hours, upper airway complications, and previous unsuccessful attempts at weaning from mechanical ventilation.[287] The failure rates following a single SBT range from 26% to 42%.[288] Objective measures of weaning readiness include hemodynamic stability, adequate gas exchange, and favorable lung mechanics, such as a RSBI of less than 105. Subjective measures encompass improvements in the underlying disease, airway patency, cough strength, and mental state.[288,289] The timing and criteria for initiating weaning are critical, as early extubation may increase the risk of re-intubation, which is linked to higher mortality rates. Re-intubation within 48 hours after extubation is associated with negative outcomes. A study involving 336 critically ill patients, all of whom were extubated using a consistent technique, provides insight into this risk. The cohort included 121 medical patients (36%), 85 surgical patients (25.2%), and 53 trauma patients (15.7%). Extubation was unsuccessful in 52 patients (15.4%), all of whom required re-intubation within 48 hours, with most occurring between 12 and 24 hours. Factors contributing to re-intubation include ineffective cough, laryngeal stridor, cardiogenic pulmonary edema, gasping, bronchospasm, muscular weakness, sensory alterations, bronchoaspiration, cardiorespiratory arrest, shock, and other complications.[291] Risk factors for extubation failure include patients with medical and interdisciplinary conditions, individuals over 70 years of age, prolonged mechanical ventilation, continuous intravenous sedation, and anemia. The causes of failure may vary, potentially including weaning failure, upper airway obstruction, insufficient cough, excessive respiratory secretions, encephalopathy, or cardiac dysfunction. Extubation failure leads to extended mechanical ventilation, prolonged ICU and hospital admissions, increased tracheostomy rates, and higher mortality rates within the hospital setting.[294]

Prediction scores, such as the Morganroth scale (Table 1) and RSBI, provide systematic guidance for ventilator weaning, although their accuracy varies among different patient demographics.[269–271] RSBI values below 105 indicate a heightened sensitivity for successful extubation, while higher values suggest a greater likelihood of weaning failure.[270] A meta-analysis has shown reasonable overall accuracy, with a sensitivity of 0.60 and a specificity of 0.68.[272]

Despite its simplicity and widespread use, the RSBI can be influenced by several factors, including fever, anxiety, discomfort, illness, or anemia, which may elevate respiratory rates and result in inaccurately high readings, thus hindering ventilator liberation. Technical and patient-related variables, such as reduced endotracheal tube diameter, female gender, and suctioning, may also affect measurements.[273] Conversely, conditions like Chronic Obstructive Pulmonary Disease (COPD) can yield inaccurately low RSBI values, especially when patients fail to trigger the ventilator during COPD exacerbations or benefit from positive pressure ventilation, as seen in Congestive Heart Failure (CHF) patients.[274,275] Neurological disorders that cause bradypnea may also lead to inaccurately low RSBI measurements.[276] The ideal threshold value may differ based on whether PSV or T-piece trials are employed, with prevailing standards recommending the use of PSV during weaning.[277,278] Research indicates that RSBI remains largely unchanged during SBTs.[279] Moreover, successive RSBI measurements taken over a 120-minute interval have not consistently identified liberation failure.[280] Fluctuations in RSBI during SBT may more accurately predict weaning success, showing high sensitivity and specificity.[281] Composite indices, such as CROP, Gluck-Corgian, and HACOR scores, combine various respiratory indicators to enhance predictive accuracy.[270,282,283] RSBI and maximal inspiratory pressure are critical indicators for successful extubation and weaning failure. The HACOR score evaluates cardiac and diaphragmatic function; however, calculating it at different times during SBT poses practical challenges, necessitating additional

validation through extensive research due to existing data limitations. The WEANS NOW score, developed in 2020, comprises eight elements related to the risk of extubation failure. Despite its thoroughness, concerns have been raised regarding its complexity and usability in bedside settings.[284] In 2021, Baptistella et al established the Extubation Predicting Score (ExPreS), which integrates both respiratory and non-respiratory factors. A score of 59 or higher indicates a substantial likelihood of successful extubation. While promising, the ExPreS requires further validation through extensive studies to confirm its efficacy as a comprehensive clinical tool (Table 1).[285]

RSBI alone has demonstrated limited diagnostic efficacy in predicting effective extubation under current weaning protocols. These findings highlight the need to revise RSBI threshold values and suggest that integrating RSBI with other predictors may enhance its utility in clinical decision-making.[286]

Weaning Prediction of Biomakers

The complex and heterogeneous nature of ARDS, which arises from both pulmonary and non-pulmonary etiologies, presents significant challenges in improving patient outcomes through randomized controlled trials. This inherent variability is frequently cited as a major factor contributing to the failure of such trials.[297] Consequently, biomarkers offer a promising strategy for addressing this heterogeneity and enhancing therapeutic success. By aiding in the understanding of ARDS variability and enriching trial populations, biomarkers facilitate the identification of appropriate patient subgroups for targeted therapies.[86]

For instance, a study investigating the sRAGE in 164 COVID-19 patients, along with convalescent individuals, non-COVID pneumonia cases, and healthy controls, demonstrated its high prognostic value. Serum sRAGE levels correlated positively with critical indicators of disease severity, including the need for oxygen therapy, the use of high-flow nasal oxygen (HFNO), MV, ARDS severity, requirements for dialysis and catecholamines, 30-day mortality, and elevated Sequential Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) scores.[298] Notably, sRAGE exhibited robust predictive capability for the requirement of MV Area Under the Curve (AUC 0.871) and mortality (AUC 0.903). Even after adjusting for confounding variables such as age, sex, comorbidities, and a SOFA score of 3 or higher, elevated sRAGE remained an independent predictor for the need for HFNO or MV.[161,298] Furthermore, analyses utilizing sRAGE and other biomarkers helped differentiate ARDS based on its origin. Patients whose ARDS resulted from direct lung injury exhibited higher concentrations of lung epithelial injury markers (plasma sRAGE and surfactant protein D (SP-D) and, simultaneously, lower levels of lung endothelial injury markers (Ang-2) and inflammatory markers (Von Willebrand factor (VWF), IL-6, and IL-8), compared to patients whose ARDS stemmed from indirect causes.[299]

PCT serves as a biomarker for the early detection of bacterial infections and sepsis across various infection sites, including pneumonia, soft tissue infections, intra-abdominal infections, and urinary tract infections, particularly within emergency and ICU settings.[300] However, its kinetic profile and overall utility require further investigation across diverse patient populations and clinical contexts.[300] In the context of ARDS specifically caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), research on circulating biomarkers of endothelial dysfunction, particularly in patients receiving anti-inflammatory treatments, revealed that conventional markers of inflammation, coagulation, and epithelial injury did not show a significant association with clinical outcomes.[301] In contrast, endothelial biomarkers, particularly plasma Neural Precursor Cell Expressed Developmentally Downregulated 9(NEDD9), were significantly linked to 60-day mortality, suggesting they act as stable indicators of immune activation.[301]

Recent studies, including those involving large COVID-19 cohorts, indicate that early levels of suPAR can predict the progression to respiratory failure and the subsequent necessity for mechanical ventilation. Elevated suPAR levels upon admission are correlated with the development of severe or critical COVID-19 and extended hospital stays. Furthermore, suPAR has been established as an independent predictor of disease severity in COVID-19.[302] While meta-analyses affirm suPAR's efficacy in prognosticating sepsis outcomes, its specific capacity to predict weaning success or duration in classical sepsis-induced ARDS necessitates dedicated future studies.

Endothelial markers such as Ang-2 and VWF are valuable predictors of mortality in patients with ARDS and those at risk. Specifically, elevated Ang-2 levels are associated with the development of ARDS in trauma-related cases, and Ang-2 levels correlate with VWF levels in predicting mortality.[27] Inflammatory biomarkers, including IL-6, CRP, and PCT, serve as sensitive indicators of systemic inflammation. These markers can predict disease severity and the need for

mechanical ventilation, especially in COVID-19 patient cohorts. However, because these inflammatory markers lack lung specificity, their utility in predicting weaning outcomes is limited when used alone.[303] Early measurement of biomarkers such as sRAGE and suPAR within the first 24 hours of ICU admission can identify patients at higher risk of progressing to invasive and prolonged mechanical ventilation. Elevated levels of sRAGE are associated with increased ARDS severity and higher mortality. Meanwhile, suPAR levels correlate with disease severity and the need for organ support, including VV-ventilation.[298] Serial monitoring of these biomarkers provides dynamic insights into a patient's evolving condition, allowing clinicians to track injury progression or recovery in real-time, thereby enhancing prognostic accuracy and supporting timely treatment modifications.[304]

The integration of biomarker assessment early in the clinical course, coupled with serial measurements, holds significant promise for individualized patient management, optimization of ventilatory support, and improved outcomes in ARDS, particularly in the context of sepsis and LI.[304] While SBT are fundamental for assessing extubation readiness, elevated levels of specific biomarkers can offer insights into persistent respiratory impairment that might not be evident through traditional physiological parameters. For example, the combined elevation of SP-D and sRAGE has shown a strong association with pulmonary edema, suggesting that epithelial injury may be a common pathway underlying alveolar-capillary barrier dysfunction in pulmonary edema. In this context, Ang-2 did not improve the predictive model, indicating that biomarkers of epithelial injury (SP-D, sRAGE) and endothelial dysfunction remain important as they are also linked to pulmonary edema in invasively ventilated patients.[305]

Elevated biomarkers indicative of ongoing lung injury, specifically those reflecting endothelial or epithelial damage, suggest residual pulmonary compromise that may not be immediately detectable through SBT. These biomarkers can assist clinicians in making more informed decisions regarding whether to delay extubation, thereby promoting individualized patient care.[306] Furthermore, biomarkers are crucial in identifying distinct ARDS subphenotypes, which allows for personalized treatment approaches.[306] The use of machine learning and advanced computational techniques enhances the understanding of these biomarkers, leading to more accurate models for predicting ARDS risk and patient outcomes.[307] For instance, a biomarker panel consisting of lung epithelium-derived proteins SP-D, sRAGE, and Clara cell secretory protein (CC-16) has shown excellent diagnostic discrimination for ARDS in patients with severe sepsis.[308]

Altered plasma levels of these biomarkers can serve as biological confirmation of an ARDS diagnosis in septic patients and may also aid in selecting appropriate candidates for clinical trials focused on reducing lung epithelial injury.[308] These multi-marker panels provide a more nuanced understanding of the underlying pathophysiological processes, enabling clinicians to tailor interventions more precisely. Integrating such biomarker panels into clinical practice holds the potential for identifying ARDS subphenotypes and facilitating personalized treatment strategies that target specific mechanisms of lung injury.[6]

Clinical Relevance of Biomakers

Interleukin-6 (IL-6)

IL-6 is a crucial pro-inflammatory cytokine that significantly contributes to the pathophysiology of sepsis and its sequelae, including ALI, ARDS, and multiple organ dysfunction syndrome (MODS) (Table 2).[309,310] In numerous studies, increased plasma IL-6 levels have been demonstrated to distinguish sepsis from non-infectious SIRS and to forecast the advancement to ARDS, indicating its potential as a novel biomarker for prompt diagnosis and management, which may decrease patient morbidity and mortality.[311] The predictive value of IL-6 as an independent marker has been questioned due to overlapping levels between survivors and non-survivors, indicating poor specificity. Additionally, inconsistencies in reported IL-6 concentrations across different studies have created uncertainty regarding appropriate therapeutic thresholds.[312] This ambiguity is heightened by evidence showing that cytokine levels, such as IL-6, are not consistently elevated in severe COVID-19 cases compared to moderate cases or critically ill ARDS/sepsis patients. Therefore, the routine use of broad immunosuppressive treatments, which have largely been ineffective in unselected ARDS patients in Phase 3 trials, remains controversial.[312]

Numerous studies emphasize the importance of serial monitoring of IL-6 levels, particularly in COVID-19 patients, where high IL-6 concentrations are identified as independent risk factors for greater disease severity and in-hospital mortality, thus

Table 2 Clinical Relevance of Emerging Biomarkers

Biomarker	Pathophysiological Role	Key Evidence	Prognostic/Diagnostic Utility	Limitations
IL-6	Central pro-inflammatory cytokine in sepsis cascade[309,310]	Elevated in sepsis, MODS, ARDS; distinguishes sepsis from SIRS; predicts ARDS onset; inhibitors (eg: tocilizumab) reduce mortality in COVID-19	Early ARDS prediction; monitoring dynamic changes improves risk stratification	High variability; poor specificity as single predictor; inconsistent thresholds
Ang-2	Endothelial injury mediator, promotes permeability[313,314]	High levels predict ARDS and mortality in sepsis and pediatric ARDS; Ang-2/Ang-1 ratio linked to poor outcomes	Superior to VWF/VEGF for endothelial dysfunction; genetic studies link high Ang-2 with doubled mortality risk	Prognostic value varies by timing and infection source; not ARDS-specific
PSP	Secreted by pancreatic acinar cells; amplifies innate immune response[315–317]	Elevated in sepsis, peritonitis, neonatal sepsis; correlates with severity and mortality; outperforms CRP and PCT in diagnosis.	Promising for early sepsis diagnosis; potential cost savings in ICU/ED; better in neonates than adults	No standardized thresholds; limited specificity; needs multimarker integration
SDC-1	Glycocalyx degradation marker; endothelial dysfunction[318–320]	Elevated early in sepsis; correlates with ARDS, AKI, mortality; dynamic rise predicts worse outcomes	Predicts fluid balance, ventilator-free days, 90-day mortality; useful with lactate	Non-specific; variability across pulmonary vs. extrapulmonary sepsis; no universal cutoff
Presepsin	Soluble CD14 subtype; reflects monocyte/ macrophage activation[321–325]	Higher in sepsis-ARDS, septic AKI, culture-negative infections; rapid rise despite antibiotics	Early diagnosis of sepsis; prognostic in elderly; complements CRP/PCT	Age-dependent accuracy; limited mortality prediction consistency
Endocan	Endothelial cell-specific proteoglycan[326,327]	Elevated in ARDS; correlates with severity and mortality; higher in non-survivors	Early severity index; better prognostic than diagnostic marker	Overlaps with PCT; limited validation
sRAGE, SP-D, KL-6	Epithelial injury markers (alveolar type I/II damage)[328–331]	Elevated sRAGE predicts mortality; SP-D correlates with ventilator dependence; KL-6 elevated in non-survivors	Panels (epithelial + endothelial) improve prognostic accuracy	Variable across ARDS etiologies; not specific to sepsis; influenced by ventilation strategies
suPAR	Reflects immune activation and systemic inflammation[332–335]	Higher in sepsis-ARDS non-survivors; threshold ≥14.01 ng/mL predicts ARDS and mortality	Reliable mortality predictor; better specificity than PCT; aids sepsis vs. SIRS discrimination	Needs standard cutoffs; still under validation

indicating the cytokine's role in predicting aggravated lung injury.[336] Research on ARDS patients indicated that serum levels of IL-6 and IL-8 were significantly elevated at presentation compared to healthy controls. Survivors showed a decrease toward baseline by Day 7, while non-survivors retained high levels.[337] Moreover, heightened plasma IL-6 levels in critically ill septic patients have been associated with an augmented risk of developing ALI and MODS, with concentrations correlating with elevated Acute Physiology and Chronic Health Evaluation (APACHE) II and SOFA scores, serving as a biomarker for the severity and onset of lung injury.[309] Baseline IL-6 levels are weak predictors of long-term outcomes when adjusted for confounding factors, but the temporal variation in IL-6 remains a significant predictor of death, supporting the need for serial monitoring in high-risk patients.[338]

Due to the constraints of utilizing IL-6 alone, researchers advocate for its integration with additional biomarkers, including PCT. The integrated dynamic evaluation of these markers is seen as more efficacious for the early identification of ARDS in individuals with MODS and for forecasting overall outcomes.[339] Moreover, clinical efficacy findings endorse targeting IL-6; a meta-analysis of individual patient data from randomized trials verified that IL-6 inhibitors markedly decreased death and enhanced intubation rates and patient discharge relative to standard care in COVID-19 patients.[340]

Angiopoietin-2

Prior research indicates that elevated early plasma Ang-2 levels serve as a predictor for ARDS and mortality in sepsis patients. Higher Ang-2 levels are linked to increased illness severity, a greater likelihood of ARDS development, and higher mortality rates, especially in patients with both ARDS and sepsis compared to those with sepsis alone.[313] Plasma Ang-2 levels have been found to be superior to other markers of endothelial damage, such as VWF and VEGF, in predicting mortality in pediatric ARDS. Elevated plasma Ang-2 is independently

linked to a higher mortality risk, with a significant trend noted from days 1 to 3, particularly among pediatric hematopoietic stem cell transplant patients, highlighting ongoing endothelial injury (Table 2).[314]

Fluctuations in Ang-2 levels over time show varying relationships depending on assessment dates, with serial evaluations failing to effectively distinguish ARDS from non-ARDS conditions, thus limiting the reliability of a single measurement for diagnostics. In critically ill septic patients, levels of sRAGE, Ang-2, and SP-D were similar between ARDS and non-ARDS groups but were higher in non-survivors than in survivors.[28] Early plasma Ang-2 levels are linked to overall disease severity, the onset of ARDS, and mortality risk, indicating that increased Ang-2 reflects general disease severity rather than ARDS-specific issues.[313] This perplexing consequence complicates the interpretation of Ang-2 elevations as exclusively symptomatic of ARDS pathobiology. Conversely, new genetic research on individuals of European descent has revealed that the primary genetic factor influencing Ang-2 levels correlates with an increased risk of ARDS, indicating that plasma Ang-2 may have a causative involvement in the onset of ARDS.[341] In cases of infection-related acute lung injury, initial Ang-2 levels were similar in survivors and non-survivors. However, a rise in plasma Ang-2 levels from day 0 to day 3 increased the likelihood of mortality by over twofold compared to declining levels, emphasizing the importance of tracking dynamic changes.[342] The prognostic significance of plasma Ang-2, in contrast to VWF, is contingent upon the presence or absence of infection as a precipitating factor for acute lung damage.[342]

Moreover, numerous studies indicate that elevated baseline Ang-2 levels correlate with a heightened risk of mortality in ARDS patients. Increased levels of circulating Ang-2 may act as an independent predictor of mortality; nevertheless, additional extensive prospective and interventional investigations are required to elucidate its diagnostic significance and causative influence on ARDS outcomes.[343] Although the research about Ang-2 is intriguing, the intricate and diverse characteristics of sepsis diminish the probability of appropriately categorizing sepsis severity using a singular biomarker.[344] Canonical Correlation Analysis, alongside Forward Selection and Random Forest techniques, identified Ang-1, Ang-2, and bicarbonate (HCO_3^-) as significant biomarkers for sepsis severity. Their diagnostic reliability was confirmed through a linear Support Vector Machine (SVM) classifier. Furthermore, these biomarkers can predict the progression of sepsis severity in pediatric patients.[344] In their study, Calfee et al measured Ang-2 levels in preserved samples from 931 participants in the ARDS Network Fluid and Catheter Treatment Trial (FACTT). They found that higher Ang-2 concentrations over time correlated significantly with worse clinical outcomes in ALI. Additionally, subgroup analyses revealed that individuals with infection-related ALI, such as pneumonia and sepsis, had elevated baseline Ang-2 levels compared to those with non-infectious ALI.[342] The research by Agrawal et al indicated that elevated plasma Ang-2 levels measured upon admission to the emergency room or ICU can effectively predict the onset of ARDS an average of 22 hours before clinical symptoms appear in critically ill patients, primarily those with infections like pneumonia or sepsis.[345]

The role of Ang-2 as a diagnostic marker for ARDS progression is not fully elucidated, with some researchers urging caution in its use due to possible confounding variables.[346] Ong et al demonstrated that the Ang-2 to Ang-1 ratio, in conjunction with established clinical and physiological variables, markedly enhanced risk prediction in patients with ALI.[347] Ongoing research is essential to elucidate the role of Ang-2 and its potential applications in clinical practice, especially considering the conflicting findings related to its diagnostic and prognostic capabilities.[346]

Pancreatic Stone Protein (PSP)

PSP levels are highly effective in diagnosing the severity of peritonitis and predicting mortality in ICU patients with sepsis-related complications, highlighting their potential importance for clinical decision-making in critical care.[315] Recent studies indicate that PSP may be effective in diagnosing sepsis, but further research is needed to determine its role in guiding early antibiotic treatment, particularly for newborns.[316] Diagnosing newborn sepsis is problematic due to the vague clinical manifestations associated with the illness (Table 2).[317] Schlapbach et al conducted an early evaluation of PSP in neonatal sepsis, revealing that infected infants exhibited significantly elevated PSP levels compared to their uninfected counterparts, with an area under the receiver operating characteristic curve (ROC) of 0.69.[348] In a study of 156 emergency department patients, PSP levels were notably elevated in those with sepsis. Multivariate regression showed PSP as an independent sepsis predictor with an AUC of 0.69. While PSP outperformed traditional markers like white blood cell (WBC) counts and CRP, its diagnostic accuracy was insufficient for it to serve as a standalone

biomarker, indicating a limitation in its clinical application.[349] A systematic study and individual-patient-level meta-analysis evaluating the accuracy of PSP for diagnosing infections in hospitalized individuals determined that PSP is a potential biomarker. With a cutoff value of 44.18 ng/mL, PSP demonstrated superior performance compared to CRP and PCT in the analyzed studies.[350]

PSP levels are elevated in various inflammatory disorders and correlate with overall illness severity and organ dysfunction, complicating the differentiation between lung-specific ARDS and systemic sepsis, which reduces the specificity of PSP as a diagnostic tool in certain clinical contexts.[351] In comparison to other biomarkers like PCT and CRP, PSP demonstrates superior performance and reliability in the diagnosis of sepsis in adults, providing potential advantages for patient management, doctors, and healthcare organizations. However, additional studies are required to define its ideal therapeutic applications and elucidate its function in conjunction with current biomarkers.[352] The potential of PSP to provide additional prognostic or predictive value beyond established severity measures like SOFA and APACHE for ARDS outcomes remains uncertain.

Meta-analysis subgroup studies show that while PSP has adequate pooled sensitivity for newborn sepsis, it has limited specificity. This suggests that PSP should be used in combination with other biomarkers, emphasizing the need for rigorous prospective studies to support this approach.[316] The expedited PSP test has shown promise in decreasing healthcare expenditures, with projected savings of $1688 per patient in the emergency room and $3315 per patient in the ICU relative to conventional care. The savings are mainly due to PSP's specificity in the emergency department and its sensitivity in the ICU.[353] Pooled sensitivity in adults is lower than in neonates, while specificity is higher in adults. This difference may be due to lower peak PSP levels in neonates, affecting diagnostic efficacy. Further research is needed to explore this disparity.[316]

Syndecan-1 (Sdc-1)

Sdc-1 serves as a biomarker for endothelial glycocalyx breakdown and is linked to poor outcomes in sepsis and septic shock. In patients experiencing septic shock, elevated plasma Sdc-1 levels during the first week correlated with the development of ARDS, particularly within the first 72 hours. Increased Sdc-1 was associated with fewer ventilator-free days, lower arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO2/FiO2), and a greater positive fluid balance.[318] Research on sepsis patients in the emergency department indicated that baseline and 6-hour Sdc-1 levels correlate with higher SOFA scores, increased fluid administration over 24–72 hours, septic shock diagnosis, the need for vasopressors or renal replacement therapy, and greater 90-day mortality rates (Table 2).[319] The specificity of Sdc-1 as a biomarker for ARDS varies with the source of infection. In a study of 262 septic patients, elevated Sdc-1 levels were linked to ARDS mainly in cases of non-pulmonary sepsis, but not in pulmonary sepsis, showing that its prognostic relevance depends on the infection's origin.[320] The situation is exacerbated by variable cutoff thresholds, as there is no established standard for predicting ARDS or ventilator outcomes, and significant overlap in Sdc-1 levels is observed between patients who develop ARDS and those who do not.[354]

Comprehensive data substantiates the predictive value of Sdc-1 in sepsis. A meta-analysis involving roughly 2318 patients indicated that elevated Sdc-1 was substantially correlated with negative composite outcomes, including septic shock, acute renal injury, and heightened mortality.[355] In pneumonia-induced sepsis, Sdc-1 showed strong correlations with neutrophil activation, respiratory failure, the necessity for MV, and 30-day mortality, in contrast to endocan.[356] Repeated assessments of Sdc-1 on days 1, 2, and 7 in the ALBIOS substudy demonstrated independent correlations with the requirement for new renal replacement therapy, coagulation failure, and 90-day mortality.[357] This indicates that the early presence of endothelial degradation products like hyaluronic acid (HA), Sdc-1, and heparan sulfate (HS) correlates positively with later organ dysfunction, allowing clinicians to use these changes for timely prediction and prevention.[358]

Sdc-1 demonstrates strong predictive capability for survival outcomes in sepsis patients. A study found that baseline Sdc-1 levels of ≥121 ng/mL were linked to reduced survival (p=0.001), and an increase of over 8 ng/mL within two days indicated a higher mortality risk (p=0.0075). The predictive performance of Sdc-1 (AUC = 0.706) improved when combined with blood lactate levels (AUC = 0.773), confirming that elevated or rising plasma Sdc-1 levels correlate with worse prognosis.[321]

Presepsin (P-SEP)

P-SEP is becoming a significant biomarker for distinguishing and forecasting outcomes in sepsis-induced ARDS. Evidence indicates that P-SEP levels are markedly higher in individuals with sepsis-related ARDS than in those with non-septic ARDS, aiding in the early differentiation between these causes.[321,322] Moreover, in patients with sepsis-related ARDS, P-SEP levels were significantly elevated in non-survivors compared to survivors ($P<0.001$), establishing P-SEP as an independent predictor of in-hospital death and highlighting its potential as a prognostic instrument.[322] The prognostic value of P-SEP is inconsistent. In a trial with 30 patients, 35% died before leaving the ICU, with no significant differences in levels of P-SEP, CRP, PCT, or IL-6 between survivors and non-survivors (Table 2).[323] The ROC curve analysis did not identify reliable mortality predictions.

However, P-SEP, alongside PCT, CRP, and IL-6, was significantly higher in patients with positive microbiological cultures, suggesting its potential as a biomarker for detecting microbiological positivity in suspected sepsis, despite poor reliability in predicting in-hospital mortality (Table 2).[323] The investigation into P-SEP's effectiveness in sepsis patients indicates that it may be a better predictor of septic acute kidney injury and ARDS in those aged 75 and older, highlighting age-related differences in its applicability.[324] P-SEP's ability to quickly rise in the bloodstream while remaining accurate even after antibiotic treatment is crucial for early sepsis identification, particularly in culture-negative cases. This characteristic underscores its importance for antimicrobial stewardship. Future studies are expected to include profiles of polymicrobial and multidrug-resistant bloodstream infections to improve the therapeutic relevance of this biomarker.[325]

Endocan

Increased endocan levels correlate with adverse outcomes in patients suffering from sepsis-induced ARDS, indicating its potential as an early marker of severity. In research, endocan concentrations assessed the day after ARDS diagnosis were markedly elevated in patients with adverse clinical trajectories compared to those with more favorable outcomes (Table 2).[326] Furthermore, at the time of ARDS admission, non-survivors demonstrated markedly elevated endocan levels compared to survivors. The diagnostic accuracy of endocan for identifying or assessing the severity of sepsis was equivalent to that of PCT; however, its predictive value for ARDS outcomes was notably superior.[359]

The investigation into the role of endocan in assessing ARDS severity suggests inconsistent results across three studies. Only one study found elevated endocan levels in patients experiencing deteriorating respiratory failure by Day 15, while the other two did not show significant correlations with ARDS severity. However, endocan levels were notably higher in all ARDS patients compared to non-ARDS individuals, with non-survivors consistently exhibiting greater levels than survivors. These findings imply that endocan may be relevant for evaluating both the severity and prognosis of ARDS, warranting further research into its therapeutic potential (Table 2).[327]

Soluble RAGE (sRAGE) and Epithelial Injury Markers (SP-D, KL-6)

A comprehensive meta-analysis found that high baseline levels of sRAGE are independently linked to increased 90-day mortality in ARDS patients, supporting the idea that alveolar epithelial injury is a key prognostic factor (Table 2).[328] The role of epithelial and endothelial damage indicators in predicting ARDS is unclear. In a study of septic patients, levels of sRAGE, SP-D, and Ang-2 showed no significant differences between those who developed ARDS and those who did not, suggesting these biomarkers may indicate mortality risk rather than predict ARDS onset in sepsis.[28]

In critically ill septic patients, sRAGE, Ang-2, and SP-D levels did not significantly differ between ARDS and non-ARDS groups but were higher in non-survivors. ARDS patients showed a trend of elevated sRAGE and SP-D levels, indicating epithelial damage in sepsis-induced ARDS. However, changes in these biomarker levels over time did not effectively distinguish between the outcomes of the groups.[28] Increased levels of the epithelial injury biomarker SP-D were observed in direct ARDS cases caused by viral and atypical pathogens, unlike ARDS from conventional bacterial pneumonia or non-pulmonary sepsis. sRAGE levels showed no significant changes based on the pathogen type. Patients with atypical pathogen-related ARDS had lower Ang-2 levels compared to those with viral or indirect ARDS. Additionally, serum IL-6 concentrations were significantly lower in patients with viral and atypical pneumonia-related

ARDS than in those with bacterial pneumonia, with atypical cases reporting the lowest levels. These findings suggest that ARDS biomarker profiles vary by underlying illness and pathogen etiology.[329]

In mechanically ventilated patients with ALI or ARDS, SP-D levels had a tendency to rise with time, especially when potentially harmful ventilation methods were employed. Baseline SP-D levels correlated with extended ventilator reliance and increased mortality rates(Table).[330] In the intrapulmonary ARDS subgroup, patients who succumbed exhibited markedly elevated serum KL-6 levels in the seven days post-diagnosis compared to survivors. In the extrapulmonary ARDS cohort, the disparity in KL-6 levels between survivors and non-survivors was significant solely on the first day following diagnosis. Patients with intra- and extrapulmonary ARDS in the mortality group demonstrated significantly elevated peak blood KL-6 levels relative to survivors.[331] Baseline plasma concentrations of CC16 and KL-6 were significantly higher in ALI/ARDS patients than in those without lung injury, while SP-D and sRAGE levels showed no significant differences. Over time, SP-D and KL-6 levels increased in ALI/ARDS patients, with this increase being mitigated by lung-protective mechanical ventilation using lower tidal volumes.[330]

Soluble Urokinase Plasminogen Activator Receptor (suPAR)

In patients with sepsis-induced ARDS, serum suPAR levels correlate significantly with illness severity and prognosis, showing positive relations with clinical severity indices like APACHE II and SOFA scores, as well as inflammatory biomarkers such as CRP, TNF-α, IL-1β, and IL-8.[332] Additionally, serum suPAR levels predict a higher risk of ARDS onset and were found to be lower in survivors compared to non-survivors.[332] In a study of 104 patients with sepsis-induced ARDS, elevated plasma suPAR concentrations in the non-survivor group demonstrated substantial prognostic value for mortality, with an AUC of 0.81 (95% confidence interval: 0.73–0.89) in ROC curve analysis.[333] A separate investigation identified suPAR as a reliable predictor of death, demonstrating significant discriminative ability through its AUC. Beyond prognostic use, suPAR has diagnostic potential; ROC analysis indicates it can differentiate between patients with sepsis plus ARDS and those with sepsis alone, achieving a sensitivity of 63.2% and specificity of 63.8% at a cut-off of 14.01 ng/mL.[332] Additionally, suPAR helps in distinguishing sepsis from SIRS (Table 2).[334] A study indicated that plasma suPAR levels remained stable during the first week of illness in both survivors and non-survivors.[335] Regression analysis showed that an APACHE II score of ≥15 and suPAR levels of ≥10.82 ng/mL were independently associated with adverse outcomes, aiding in patient classification by severity with different fatality rates.[335] Compared to PCT, suPAR not only offers similar clinical guidance but also exhibits superior specificity.[334] Therefore, combining the APACHE II score and suPAR levels may provide a more effective predictive approach for assessing mortality risk in septic patients.[335]

Guideline-Baseline Methodologies

These treatments are underpinned by rigorous clinical studies and established protocols, providing a core framework for incorporating new medications. MV employs low tidal volume techniques, typically around 6 mL/kg of anticipated body weight, with a plateau pressure limit of ≤30 cm H_2O. It also advocates for elevated positive end-expiratory pressure (PEEP) in mild to severe cases to prevent volutrauma and barotrauma.[360] In moderate to severe ARDS, the prompt implementation of prone positioning for at least 12 to 16 hours daily in ventilated patients has demonstrated a considerable reduction in mortality.[361]

Neuromuscular blockade (NMB) is recommended in the initial stages of severe ARDS to enhance patient-ventilator synchronization and mitigate ventilator-induced lung injury (VILI). Data support the preference for occasional boluses over continuous infusion, accompanied by meticulous monitoring.[362] In moderate to severe ARDS, recruitment maneuvers and PEEP titration procedures tailored to individual lung mechanics are recommended to enhance alveolar recruitment. In milder cases, excessive PEEP should be avoided (Table 3).[363]

Fluid management is essential; a conservative fluid strategy following initial resuscitation may reduce pulmonary edema and improve outcomes. Dynamic parameters are favored over static measurements to guide treatment.[360] Prompt treatment with corticosteroids, such as dexamethasone, in certain settings of ARDS, particularly moderate-to-severe or COVID-19-related ARDS, has shown a reduction in mechanical ventilation duration and may lower mortality rates, although the precise types, dosages, and timing of administration can vary.[362]

Table 3 Guideline-Based Core Strategies Management

Intervention	Mechanism/Purpose	Evidence/Outcomes	Limitations/Considerations	References
Low tidal volume ventilation (6 mL/kg)	Reduces volutrauma and barotrauma	Decrease mortality and VILI	Requires careful monitoring; plateau pressure ≤30 cm H_2O	[360,361]
Prone Positioning (12–16 h/day)	Improves oxygenation and alveolar recruitment	Significant mortality reduction in moderate to severe ARDS	Logistically challenging	[361]
NMB	Enhance patient ventilator synchrony; reduces VILI	Intermittent boluses preferred over continuous infusion	Risk of prolonged paralysis; require monitoring	[362]
PEEP titration/ recruitment maneuvers	Optimizes alveolar recruitment	Improves oxygenation; individualized approach recommended	Excessive PEEP may harm mild ARDS patients	[363]
Fluid Management	Minimizes Pulmonary Edema	Enhances Oxygenation and Outcomes	Must balance with hemodynamic stability	[360]
Corticosteroid Administration	Reduces inflammation and ventilation duration	May lower mortality in moderate to severe or COVID-19 ARDS	Timing,dose,and patient selection vary; infection risk	[363]
ECMO	Supporting oxygenation in refractory cases	Life saving in severe ARDS when conventional strategies fail	Requires specialized centers, high resource use	[362]

Abbreviations: ECMO, Extracorporeal Membrane Oxygenation; NMB, Neuromuscular Blockade; PEEP, Positive End-Expiratory Pressure.

Ultimately, for patients with severe ARDS who do not respond to conventional ventilation, venovenous extracorporeal membrane oxygenation (ECMO) may be considered in facilities with sufficient expertise. These evidence-based techniques collectively endorse a holistic approach to ARDS management, combining contemporary best practices with ongoing innovations (Table 3).[362]

Novel Therapeutic and Experimental Targets

In sepsis and ARDS, damage to the pulmonary microvascular endothelium leads to capillary leakage, alveolar flooding, and impaired gas exchange. Therapeutic approaches designed to stabilize the endothelial barrier have shown potential in preclinical research. One strategy involves modulating the Ang-1/Ang-2–Tie2 axis, which has demonstrated efficacy in reducing vascular permeability and inflammation in experimental models (Table 4).[364] Sphingosine-1-phosphate (S-1P), through its G-protein-coupled receptor $S1P_1$, is essential for maintaining lung endothelial integrity. It triggers signaling pathways that engage Rho and Rac1, reorganizing the endothelial cytoskeleton to create cortical actin rings. This process strengthens focal adhesions and intercellular junctions, including cadherins and catenins. Consequently, this coordinated mechanism reduces vascular permeability and preserves the integrity of the alveolar–capillary barrier, thereby preventing alveolar flooding in ARDS models (Table 4).[365,366] Moreover, statins have shown the ability to protect the lungs by maintaining endothelial integrity, reducing vascular permeability, and providing anti-inflammatory and antithrombotic effects.[367] In endotoxin-induced lung damage models, simvastatin decreased protein permeability and pulmonary edema, restricted neutrophil migration, and reduced cytokine production from endothelial cells, including IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and regulated upon activation, normal T cell expressed and secreted (RANTES) (Table 4).[368] These data suggest the efficacy of endothelial-targeted treatments in alleviating lung damage associated with sepsis-induced ARDS.

The modulation of neutrophil migration and activation is a crucial therapeutic target in the treatment of ARDS. In patients with ARDS, a notable concentration of neutrophils is observed in bronchoalveolar lavage (BAL) fluid, and the sustained elevation of these neutrophil levels is closely correlated with impaired gas exchange and worse clinical outcomes.[369] A primary mechanism governing neutrophil survival in hypoxic environments is the hypoxia-inducible factor (HIF) oxygen-sensing pathway. HIF has shown the potential to prolong neutrophil viability under hypoxic conditions, which are prevalent in inflamed pulmonary tissue. The function and expression of HIF are meticulously controlled by oxygen-sensitive prolyl hydroxylases (PHD1-3), which regulate HIF stability and transcriptional activity in response to oxygen levels.[370] Understanding these processes underscores the importance of focusing on neutrophil activation and survival pathways to potentially mitigate inflammation and tissue injury in ARDS.

Table 4 Novel Therapeutic and Experimental Targets

Therapeutic Strategy	Mechanism of Action	Evidence	Limitations	Clinical Implications	References
Angiopoietin-1/ Angiopoietin-2 Modulation	Stabilizes endothelial barrier, reduces vascular permeability	Preclinical studies show reduced vascular leak and inflammation in experimental models	Limited to preclinical data; human efficacy and safety not fully established	Potential to preserve alveolar-capillary integrity; experimental therapeutic approach	[364]
S1P	Endothelial integrity by activating signaling pathways that reinforce intercellular junctions.	Preclinical ARDS models demonstrate reduced alveolar flooding	Clinical application and long-term safety data are lacking; requires further investigation in human	Maintains lung endothelial integrity; potential adjunct therapy	[365,366]
Statins (Simvastatin)	Anti-inflammatory, antithrombotic, reduces vascular permeability	Endotoxin-induced lung injury models show decreased edema and cytokine release	Clinical trials show mixed results; effectiveness in established ARDS limited	May protect lung function in sepsis; clinical translation under investigation	[367,368]
Neutrophil Modulation	Regulates neutrophil survival and activation under hypoxia.	Correlated with improved gas exchange and reduced tissue injury	Potential immunosuppression; safety of HIF modulation in humans untested	Targeting neutrophil activity may limit pulmonary inflammation	[369,370]
Immunomodulation and Anti-Cytokine Therapies	Inhibit IL-6, IL-1, TNF-α to reduce cytokine storm	Tocilizumab decreases mortality in COVID-19 ARDS; other agents under study	Effectiveness varies by patient and timing; risk of secondary infections; limited evidence outside COVID-19	Adjunct therapy in hyperinflammatory ARDS; personalized use required	[371,374]
MSC Therapy	Promotes repair of epithelial and endothelial cells and modulates inflammation.	Initial trials indicate safety and preliminary clinical benefit in ARDS patients	Limited clinical efficacy observed in early studies; larger, well-designed trials are necessary for validation.	Potential therapy to improve lung repair and ventilation outcomes	[375]
Coagulation/ Fibrinolysis modulation	Target TF, heparin, antithrombin, streptokinase	Preclinical and early clinical studies show reduced fibrin deposition, improved oxygenation	Risk of bleeding complications; optimal dosing and timing unclear; limited large-scale trials	May enhance alveolar perfusion and reduce ventilation duration	[376,381]
Adjunct Therapies (eg: α1-AR Antagonists)	Prevents hyperinflammation and mortality in lower respiratory tract infections.	Observational studies suggest reduced risk of mechanical ventilation and death in patients exposed to α1-AR antagonists	Limited prospective data; requires further validation through controlled trials.	Potential strategy to mitigate severe inflammatory responses; clinical validation required	[382]

Abbreviations: S1P, Sphingosine-1-Phosphate; MSC, Mesenchymal Stem Cell.

Immunomodulation and anti-cytokine medications have become significant in the treatment of sepsis and ARDS, particularly during the hyperinflammatory phase characterized by elevated concentrations of cytokines such as IL-6, IL-1, and TNF-α. The overproduction of cytokines, along with immunological dysregulation, substantially contributes to lung damage. Targeted inhibition of these inflammatory mediators presents a potential approach to reduce tissue damage. In the context of COVID-19-related ARDS, immunomodulatory treatments have become essential adjuncts, exhibiting the ability to mitigate the cytokine storm and reduce lethal lung injury. Early administration of tocilizumab, an IL-6 receptor antagonist, has been shown to dramatically decrease mortality (Table 1)[371] however, the effectiveness of baricitinib remains less certain.[372] Moreover, additional cytokine inhibitors, including sarilumab, canakinumab, adalimumab, and itolizumab,

as well as agents such as dexamethasone and colchicine, have demonstrated potential advantages in decreasing mortality or altering disease progression; however, further validation through comprehensive studies is required (Table 4).[373,374] Furthermore, combination therapies targeting both viral replication and immunological dysregulation, such as remdesivir paired with baricitinib or repurposed medication combinations like sirolimus and dactinomycin, are currently under investigation to enhance clinical outcomes.[383]

Mesenchymal stem cell (MSC) treatment has garnered attention for its immunomodulatory capabilities, capacity to facilitate epithelial and endothelial repair, regulation of inflammation, and potential to improve alveolar fluid clearance. Initial clinical studies have primarily focused on evaluating the safety and efficacy of MSCs in patients with ARDS. Zheng et al first conducted a trial using allogeneic adipose-derived MSCs in 12 patients, revealing no therapeutic effect while confirming safety.[375] Subsequently, Wilson et al conducted a Phase 1 study using bone marrow-derived MSCs in nine patients with moderate-to-severe ARDS, reaffirming the intervention's safety but acknowledging specific limitations. Recently, Matthay et al published findings from a multicenter, double-blind, Phase 2a study comprising 60 ventilated patients with ARDS. This research indicated that a single intravenous infusion of MSCs was safe and exhibited initial indications of clinical benefit, including improvements in APACHE II scores and ventilatory parameters, suggesting prospective therapeutic efficacy (Table 4).[375]

ARDS often manifests with elements of coagulopathy, microthrombosis, and fibrin accumulation in the alveoli. Medications that regulate coagulation and fibrinolysis may enhance alveolar gas exchange, whereas nebulized medications provide localized distribution to the lungs. Tissue factor (TF), a glycoprotein that increases during pulmonary inflammation, significantly contributes to fibrin deposition and exacerbates inflammation in ARDS. Increased blood levels of TF have been associated with higher mortality rates.[376] In a Phase 1 placebo-controlled study, the anti-TF antibody ALT-836 demonstrated safety in patients with ARDS.[377] A phase 2 study involving 150 septic ARDS patients was completed in 2013, although effectiveness data remain unreported. Moreover, heparin and antithrombin have demonstrated the ability to mitigate inflammation and ALI in preclinical animal studies without negatively impacting systemic coagulation.[378] A study of 50 critically ill patients demonstrated that nebulized heparin reduced the duration of mechanical ventilation and improved alveolar perfusion and carbon dioxide removal in patients undergoing heart surgery.[379,380] A phase 3 study indicated that nebulized streptokinase enhanced oxygenation and lung compliance in 60 patients with late-phase severe ARDS, suggesting its potential as a rescue treatment (Table 4).[381] Adjunct therapy, encompassing drugs for diverse conditions, may affect the development of ARDS. Studies indicate that alpha-1 adrenergic receptor (α1-AR) antagonists can mitigate hyperinflammation and decrease mortality in murine models.[382] Patients using α1-AR antagonists exhibited a 34% decrease in the likelihood of requiring mechanical ventilation and mortality. Additional trials are required to determine whether this medication effectively mitigates hyperinflammation and mortality in lower respiratory tract infections (Table 4).[382]

Futures Guidance And Individualized Medication

The future treatment of sepsis-induced ARDS is progressively emphasizing biomarker-guided therapy and precision medicine, moving away from the conventional "one-size-fits-all" approach. Circulating and respiratory biomarkers, including Ang-2, sRAGE, suPAR, and PSP, show promise in risk stratification, the identification of subphenotypes (hyperinflammatory vs. hypoinflammatory), and the prediction of important events, such as ventilator weaning success or mortality rates. The amalgamation of these biomarkers with clinical assessments and sophisticated computer models may enable tailored therapeutic approaches, optimizing the timing and selection of therapies such as corticosteroids, statins, MSCs, and immune modulators.

Notwithstanding these promising developments, many research deficiencies remain. Numerous biomarker investigations are limited by inadequate sample sizes, varied demographics, and insufficient validation across diverse clinical settings. The integration of potential biomarkers into standard clinical practice is impeded by inconsistencies in testing techniques, ambiguous cutoff values, and questionable cost-effectiveness. Future investigations should prioritize extensive, multicenter trials to validate biomarker panels, develop point-of-care tests, and explore the integration of genomics, proteomics, and machine learning into bedside decision-making. Such efforts might facilitate the development of truly personalized medicine in the treatment of sepsis-induced ARDS, ultimately enhancing outcomes in this potentially fatal condition.

Conclusion

Sepsis poses a significant global health challenge, impacting millions and serving as a major contributor to the development of ARDS. The intricate relationship between sepsis and ARDS results in severe outcomes, including elevated mortality rates and extended mechanical ventilation, highlighting the urgent need for effective management strategies. While advancements have been made in understanding the underlying mechanisms, notable gaps persist in the clinical application of biomarkers for predicting weaning success in this vulnerable population. The use of circulating and respiratory biomarkers presents a promising opportunity to enhance clinical decision-making and improve patient outcomes. By incorporating these indicators into standard practice, healthcare providers may more effectively navigate the complexities of weaning protocols, ultimately decreasing the duration of mechanical ventilation and lowering the risk of extubation failures. Ultimately, the implementation of validated biomarker-guided strategies could transform clinical management, leading to reduced ventilation days, fewer extubation failures, and improved survival rates in this high-risk population.

Abbreviations

BSF-2, B-cell stimulatory factor 2 malondialdehyde; LPS, Lipopolysaccharide; VE-PTP, Vascular Endothelial Protein Tyrosine Phosphatase; VE, Vascular Endothelial; ROS, reactive oxygen species; PRR, Pattern Recognition Receptors; DAMP, Damage-Associated Molecular Patterns; PAMPs, Pathogen-Associated Molecular Patterns; AUC, Area Under the Curve; ALI, Acute Lung Injury; Ang-1, Angiopoietin-1; Ang-2, Angiopoietin-2; APACHE, Acute Physiology and Chronic Health Evaluation; AR, Acute Respiratory; ARDS, Acute Respiratory Distress Syndrome; BAL, Bronchoalveolar Lavage; CHF, Congestive Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, Coronavirus Disease 2019; CRP, C-Reactive Protein; DAMPs, Damage-Associated Molecular Patterns; ECMO, Extracorporeal Membrane Oxygenation; ExPreS, Extubation Predicting Score; G-CSF, Granulocyte Colony-Stimulating Factor; GTP, Guanosine Triphosphate; GPX4, Glutathione Peroxidase 4; HIF, Hypoxia-Inducible Factor; HMGB1, High Mobility Group Box 1; IL-1, Interleukin-1; IL-1β, Interleukin-1 Beta; IL-6, Interleukin-6; IMV, Intermittent Mandatory Ventilation; MCP-1, Monocyte Chemoattractant Protein-1; MSC, Mesenchymal Stem Cell; NMB, Neuromuscular Blockade; NEDD9, Neural Precursor Cell Expressed Developmentally Downregulated 9; PAMPs, Pathogen-Associated Molecular Patterns; PaO2/FiO2, Arterial Oxygen Partial Pressure to Fractional Inspired Oxygen Ratio; PEEP, Positive End-Expiratory Pressure; PCT, Procalcitonin; PSP, Pancreatic Stone Protein; PSV, Pressure Support Ventilation; RANTES, Regulated upon Activation, Normal T Cell Expressed and Secreted; RSBI, Rapid Shallow Breathing Index; sCD14, Soluble CD14; sRAGE, Soluble Receptor for Advanced Glycation End-products; S-1P, Sphingosine-1-Phosphate; SBT, Spontaneous Breathing Trial; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment; SP-D, Surfactant Protein D; suPAR, Soluble Urokinase Plasminogen Activator Receptor; TF, Tissue Factor; TNF-α, Tumor Necrosis Factor Alpha; TLR, Toll-like Receptor; VAP, Ventilator-Associated Pneumonia; VEGF, Vascular Endothelial Growth Factor; VILI, Ventilator-Induced Lung Injury; COPD, Chronic Obstructive Pulmonary Disease; SIRS, Systemic Inflammatory Response Syndrome; MODS, Multiple Organ Dysfunction Syndrome; VWF, von Willebrand factor; VEGF, Vascular Endothelial Growth Factor; sRAGE, soluble receptor for advanced glycation end-products; PSP, Pancreatic stone protein; ED, Emergency Department; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; SDC-1, Syndecan-1; SP-D, surfactant protein D; SuPAR, Soluble urokinase plasminogen activator receptor; IMV, Intermittent Mandatory Ventilation; SIMV, Synchronized Intermittent Mandatory Ventilation; SBT, Spontaneous Breathing Trial; CC16, Clara Cell protein16; KL-6, Krebs von den Lungen-6; PSV, Pressure Support Ventilation; ExPreS, Extubation Predicting Score; HFNO, High-Flow Nasal Oxygen; PEEP, Positive End-Expiratory Pressure; NMB, Neuromuscular blockade; VILI, Ventilator-Induced Lung Injury; MSC, Mesenchymal stem cell.

Data Sharing Statement

As this review relies solely on previously published data, data availability does not apply.

Ethical Approval

This study did not include original research involving humans or animals; hence, ethical approval was not required.

Author Contributions

Professor Sun and Professor Liu contributed to the conceptualization and supervision of the study. Dr. Emery contributed to the study design and execution, while Dr. Geoffrey contributed to the study design and the writing of the original draft. All authors participated in writing, review, and editing of the manuscript. Each author has given final approval for the version to be published, agreed on the journal to which the article has been submitted, and accepts accountability for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest.

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